Supplementary Table 1. Descriptive statistics for all samples.

	Stage 1				Stage 2											
					GERAD 2										AD-IG	deCODE
	GERAD 1	EADI1	ADNI	TGEN1	Total GERAD2 Sample	MRC	ART	Belgium	Bonn	Caerphilly	UCL-PRION	Laser	Greece	Munich		
Genotyping Platform	Illumina 610,550 & 300	Illumina 610	Illumina 610	Affymetrix 500K	Sequenom										Illumina 550 & 610	Illumina 300, CNV370
AD Cases																
n	3941[§]	2025[§]	151[§]	571[§]	3262	292[§]	628[§]	1078[§]	347[§]	51[§]	92[§]	42[§]	404[§]	328[§]	709[§]	925[§]
% Female	62.7	66.0	47.0	52.0	64.4	63.5	61.3	66.2	79.3	0	57.1	69.0	64.6	66.8	56.1	65.6
Age at onset, Mean	73.2	68.3	73.5	N/A	72.9	75.7	70.6‡	74.9	70.3	N/A	61.2	N/A	69.0‡	70.5	69.5	N/A
Age at Interview/ascertainment, Mean	78.6	73.7	76.6	81.0	77.7	81.1	78.4†	78.6	76.2	N/A	N/A	79.3	76.7	73.2	72.8	N/A
Age at death, Mean	80.4*	N/A	N/A	N/A	81.6	N/A	81.6†	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Controls																
n	7848[#,††,‡‡]	5328[#]	177[#]	332[**,††]	3320	45[#]	375[#,**]	593[#]	896[**]	0	0	0	147[‡‡]	858[#]	971[‡‡]	612[**]
% Female	65.8	61	44.6	63	56.1	65.0	61.4	57.4	66.4	N/A	N/A	N/A	53.1	39.3	48	60.6
Age at Interview/ascertainment, Mean	55.6	73.8	78.0	80	73.7	76.4	75.3†	73.5	79.5	N/A	N/A	N/A	73.2	66.0	47.9	N/A
Age at death, Mean	80.4*	N/A	N/A	N/A	76.7	N/A	76.7†	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

	Stage 3													
	EADI2			Mayo2							CHARGE			
	Finland	Italy	Spain	Jacksonville	Rochester	Autopsy	NCRAD	Norway	Poland	ART	CHS	FHS	Rotterdam	AGES
Genotyping Platform	Sequenom			TaqMan®							Illumina CNV370	Affymetrix 500+50K Gene Focused Panel	Illumina 550	Illumina CNV370
AD Cases														
n	563[§]	1460[§]	728[§]	849[¶]	587[¶]	580[§]	702[¶]	345[¶]	479[§]	626[§]	93[¶]	52[§]	171[§]	78[¶]
% Female	68.0	68.0	57.0	62.0	60.6	58.5	64.8	69.9	66.2	55.2	53	81	75	50
Age at onset, Mean	71.3	73.8	72.5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Age at Interview/ascertainment, Mean	N/A	76.6	75.3	77.8	80.2	N/A	75.2	80.2	76.7	75.8	80	87	84	81
Age at death, Mean	N/A	N/A	N/A	N/A	N/A	81.1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Controls														
n	529[c]	1262[#]	829[#]	1303[**]	2390[**]	355[††]	209[**]	553[‡‡,#]	182[**]	742[#,**]	2429[**]	2091[#]	5700[**]	2684[#]
% Female	58.0	55.0	62.0	57.3	53.7	42.5	61.7	59.9	76.9	49.9	62	57	59	58
Age at Interview/ascertainment, Mean	69.0	72.3	76.9	79.3	78.3	N/A	78.3	75.4	73.0	76.3	75	76	69	76
Age at death, Mean	N/A	N/A	N/A	N/A	N/A	75.8	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Incidence studies														
Cohort at risk											2429	806	5700	
% Female											62	60	59	
Age at start											75	82	69	
Incident AD cases											435[§]	76[§]	462[§]	

* Data only available for a proportion of the sample † Age at interview not available for 438 AD cases and 104 controls. Age at death is provided for these subjects where available. ‡ Age at onset data only available for less than 75% of the sample. § diagnosed according to NINCDS-ADRDA, DSM or CERAD Criteria for probable AD or definite AD. ¶ diagnosed according to NINCDS-ADRDA, or DSM Criteria for possible or probable AD. # Screened for dementia using the MMSE. ** Control screened for dementia using the modified MMSE, TICS-M, Geriatric Mental Schedule, Cognitive Performance Scale, SIDAM or Clinical Dementia Rating Scale. †† Neuropathological conifrmed controls according to CERAD criteria or Braak and Braak Staging. ‡‡ Unscreened population controls.

Supplementary Table 2. Results for SNPs with P≤1x10^{-5} in Stage 1

SNP	Closest Gene	CHR	BP	A1	A2	Stage 1 Datasets								Stage 1		Stage 1 Sample Size		SNP selected for Stage 2?	Notes
						GERAD1		EADI1		ADNI		TGEN1							
						OR	P	OR	P	OR	P	OR	P	OR	P	Cases	Controls		
rs4844579	*C4BPA*	1	207,377,891	T	C	1.12	3.6E-03	1.17	5.8E-04	1.28	2.0E-01	1.18	1.6E-01	1.14	1.9E-06	6,080	12,297	No	SNP was not selected for Stage 2 as it is located at the *CR1* locus
rs6673080	*C4BPA*	1	207,390,204	T	C	1.11	4.8E-03	1.17	6.5E-04	1.27	2.2E-01	1.20	1.2E-01	1.14	2.5E-06	6,080	12,297	No	SNP was not selected for Stage 2 as it is located at the *CR1* locus
rs6540433	*CR2*	1	207,653,395	C	A	1.12	1.8E-03	1.18	8.0E-04	1.45	1.0E-01	1.39	2.6E-02	1.16	5.1E-07	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *CR1* locus
rs4310446	*CR1*	1	207,676,604	C	T	1.10	1.0E-02	1.19	2.1E-04	1.44	7.8E-02	1.25	9.4E-02	1.14	1.8E-06	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *CR1* locus
rs3818361	*CR1*	1	207,784,968	A	G	1.16	3.7E-05	1.28	8.5E-08	1.58	2.4E-02	1.20	1.4E-01	1.21	3.2E-12	6,688	13,251	Yes	SNP is most significant at the *CR1* locus.
rs6701713	*CR1*	1	207,786,289	A	G	1.17	8.7E-06	1.25	1.1E-06	1.58	2.4E-02	1.20	1.4E-01	1.20	6.0E-12	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *CR1* locus
rs1408077	*CR1*	1	207,804,141	A	C	1.17	8.3E-06	1.25	1.7E-06	1.66	1.5E-02	1.20	1.4E-01	1.20	6.4E-12	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *CR1* locus
rs744373	*BIN1*	2	127,894,615	G	A	1.16	1.4E-06	1.15	5.7E-04	1.13	4.4E-01	1.35	1.7E-02	1.17	1.5E-10	6,688	12,716	Yes	SNP is most significant at the *BIN1* locus.
rs11136000	*CLU*	8	27,464,519	T	C	0.84	1.4E-09	0.81	5.2E-08	0.93	6.4E-01	0.80	1.0E-01	0.83	2.0E-16	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *CLU* locus
rs10761558	*CDK1*	10	62,523,470	A	G	1.26	1.6E-05	1.12	4.4E-03	1.12	5.1E-01	1.07	5.4E-01	1.16	1.0E-06	6,080	7,062	Yes	
rs667897	*MS4A6A*	11	59,936,979	G	A	0.89	2.5E-05	0.94	7.0E-02	0.96	7.8E-01	0.76	6.4E-03	0.90	8.7E-07	6,688	13,685	No	SNP was not selected for Stage 2 as a proxy SNP rs610932 (r^2=0.88) was genotyped in Stage 2
rs610932	*MS4A6A*	11	59,939,307	T	G	0.87	1.5E-06	0.93	4.6E-02	0.88	4.5E-01	0.74	2.8E-03	0.88	1.8E-08	6,688	13,251	Yes	
rs662196	*MS4A6A*	11	59,942,757	C	T	0.88	5.2E-06	0.95	1.5E-01	0.92	6.2E-01	0.75	3.9E-03	0.89	2.5E-07	6,688	13,685	No	SNP was not selected for Stage 2 as a proxy SNP rs610932 (r^2=0.934) was genotyped in Stage 2
rs583791	*MS4A6A*	11	59,947,252	C	T	0.88	5.3E-06	0.95	1.6E-01	0.92	6.2E-01	0.75	3.9E-03	0.90	7.4E-07	6,688	13,685	No	SNP was not selected for Stage 2 as a proxy SNP rs610932 (r^2=0.934) was genotyped in Stage 2
rs7926344	*MS4A6A*	11	59,962,166	A	G	0.88	7.9E-05	0.95	1.4E-01	0.91	5.8E-01	0.72	1.3E-03	0.90	2.4E-06	6,080	12,297	No	SNP was not selected for Stage 2 as a proxy SNP rs610932 (r^2=0.782) was genotyped in Stage 2
rs670139	*MS4A4E*	11	59,971,795	T	G	1.13	8.7E-05	1.06	1.2E-01	1.08	6.6E-01	1.26	2.3E-02	1.11	1.0E-05	6,080	11,863	Yes	SNP was selected as a proxy SNP for rs676309 (r^2=1)
rs7929589	*MS4A4E*	11	59,975,078	T	C	0.88	8.3E-05	0.95	1.7E-01	0.89	4.7E-01	0.72	1.1E-03	0.91	6.0E-06	6,080	12,297	No	SNP was not selected for Stage 2 as a proxy SNP rs610932 (r^2=0.721) was genotyped in Stage 2
rs676309	*MS4A4E*	11	60,001,573	C	T	1.14	6.3E-06	1.04	2.1E-01	1.07	6.7E-01	1.27	2.0E-02	1.11	2.0E-06	6,688	13,685	No	Not possible to design a multiplex assay including this SNP; a proxy SNP rs670139 (r^2=1) was genotyped in Stage 2
rs1562990	*MS4A4A*	11	60,023,087	C	A	0.88	1.0E-05	0.96	2.4E-01	0.96	7.8E-01	0.71	6.7E-04	0.90	1.4E-06	6,688	13,685	No	SNP was not selected for Stage 2 as a proxy SNP rs610932 (r^2=0.618) was genotyped in Stage 2
rs677909	*PICALM*	11	85,757,589	C	T	0.88	1.6E-05	0.88	3.0E-03	1.02	9.0E-01	0.91	3.5E-01	0.88	1.4E-07	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *PICALM* locus
rs536841	*PICALM*	11	85,787,824	C	T	0.86	3.5E-06	0.88	3.7E-03	0.98	9.3E-01	0.90	3.4E-01	0.87	3.6E-08	6,080	12,297	No	SNP was not selected for Stage 2 as it is located at the *PICALM* locus
rs541458	*PICALM*	11	85,788,351	C	T	0.87	2.3E-06	0.88	3.5E-03	1.00	9.9E-01	0.90	3.4E-01	0.87	1.9E-08	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *PICALM* locus
rs1237999	*PICALM*	11	85,815,030	G	A	0.87	1.1E-06	0.94	1.1E-01	1.03	8.4E-01	0.91	3.6E-01	0.90	1.7E-06	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *PICALM* locus
rs543293	*PICALM*	11	85,820,077	A	G	0.86	6.9E-07	0.93	9.1E-02	0.92	6.4E-01	0.88	2.2E-01	0.89	2.7E-07	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *PICALM* locus
rs659023	*PICALM*	11	85,824,859	A	G	0.86	3.6E-06	0.93	7.1E-02	1.07	7.0E-01	0.93	4.5E-01	0.89	3.1E-06	6,080	12,297	No	SNP was not selected for Stage 2 as it is located at the *PICALM* locus
rs7941541	*PICALM*	11	85,858,538	G	A	0.84	2.1E-07	0.91	2.4E-02	0.90	5.4E-01	0.84	1.0E-01	0.87	9.0E-09	6,080	12,297	No	SNP was not selected for Stage 2 as it is located at the *PICALM* locus
rs3851179	*PICALM*	11	85,868,640	T	C	0.85	1.9E-08	0.92	3.1E-02	0.83	2.8E-01	0.82	6.3E-02	0.87	7.2E-10	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *PICALM* locus
rs10501927	*CNTN5*	11	99,757,729	G	T	1.16	2.3E-05	1.10	1.2E-02	1.38	1.0E-01	1.00	1.0E+00	1.14	8.0E-07	6,688	13,251	Yes	
rs3809278	*CUX2*	12	111,725,185	A	C	1.12	5.4E-03	1.23	1.0E-04	1.34	2.3E-01	1.23	1.5E-01	1.17	1.1E-06	6,688	13,685	Yes	
rs739565	*C16orf88*	16	19,716,505	A	G	1.07	3.1E-02	1.19	9.9E-06	1.01	9.5E-01	1.38	3.6E-02	1.11	3.9E-06	6,688	13,251	Yes	
rs1858973	*IQCK*	16	19,743,649	C	T	0.91	1.5E-02	0.80	1.6E-05	0.92	6.8E-01	0.73	1.4E-02	0.86	7.2E-07	6,688	13,251	Yes	
rs4782279	*IQCK*	16	19,759,007	C	A	0.92	2.1E-02	0.80	5.4E-06	1.03	9.0E-01	0.73	1.2E-02	0.87	7.7E-07	6,688	13,251	Yes	
rs9931167	*IQCK*	16	19,792,598	T	C	0.93	8.0E-02	0.80	2.3E-05	0.92	7.0E-01	0.71	5.8E-03	0.87	6.0E-06	6,080	12,297	No	SNP was not selected for Stage 2 as a proxy SNP rs4782279 (r^2=0.945) was genotyped in Stage 2
rs7191155	*IQCK*	16	19,800,213	C	T	0.91	1.1E-02	0.80	2.4E-05	0.92	6.8E-01	0.71	5.9E-03	0.86	3.6E-07	6,688	13,251	Yes	
rs3764650	*ABCA7*	19	1,046,520	G	T	1.24	4.1E-05	1.21	4.0E-03	1.01	9.7E-01	N/A	N/A	1.22	2.6E-07	5,509	11,531	Yes	
rs7255066	*PVR*	19	45,146,103	C	T	0.88	7.4E-05	0.90	3.4E-03	0.70	2.9E-02	1.35	1.4E-01	0.89	5.9E-07	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs2927488	*CEACAM16*	19	45,231,478	A	G	0.91	4.7E-03	0.82	6.5E-06	1.00	9.9E-01	1.14	4.6E-01	0.88	1.8E-06	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs2965101	*BCL3*	19	45,237,812	C	T	0.86	4.6E-07	0.78	1.9E-09	1.00	9.9E-01	1.11	4.9E-01	0.84	2.8E-13	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs2927438	*BCL3*	19	45,242,107	A	G	1.25	3.0E-11	1.21	2.9E-05	1.25	2.2E-01	N/A	N/A	1.23	2.3E-15	6,117	13,353	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs4803750	*BCL3*	19	45,247,627	G	A	0.77	2.8E-05	0.73	5.7E-04	0.83	6.3E-01	N/A	N/A	0.75	5.9E-08	5,509	11,965	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs8103315	*BCL3*	19	45,254,168	A	C	1.24	2.9E-07	1.28	4.1E-06	1.63	2.8E-02	N/A	N/A	1.26	8.5E-13	5,509	11,965	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs1871045	*BCAM*	19	45,326,768	T	C	0.89	1.2E-04	0.89	2.6E-03	1.10	5.5E-01	0.86	1.5E-01	0.89	7.6E-07	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs10402271	*BCAM*	19	45,329,214	G	T	1.36	1.5E-26	1.36	8.5E-15	0.94	6.9E-01	1.22	5.5E-02	1.34	7.2E-39	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs1871047	*PVRL2*	19	45,351,746	G	A	0.85	1.3E-08	0.82	2.0E-06	0.94	6.9E-01	0.84	2.6E-01	0.84	9.8E-14	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs377702	*PVRL2*	19	45,362,667	A	G	1.20	8.4E-11	1.10	1.2E-02	1.07	6.9E-01	N/A	N/A	1.16	1.8E-11	6,117	13,353	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs12610605	*PVRL2*	19	45,370,838	A	G	0.81	7.7E-07	0.81	6.8E-05	0.99	9.7E-01	N/A	N/A	0.81	3.3E-10	5,509	11,965	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs6859	*PVRL2*	19	45,382,034	A	G	1.46	7.0E-41	1.31	3.8E-13	1.39	3.9E-02	N/A	N/A	1.40	1.3E-52	6,117	13,353	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs157580	*TOMM40*	19	45,395,266	G	A	0.63	9.6E-54	0.62	5.1E-33	0.46	1.7E-05	N/A	N/A	0.62	3.7E-90	6,117	13,353	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs2075650	*TOMM40*	19	45,395,619	G	A	2.53	1.8E-157	3.17	1.2E-130	3.07	6.3E-08	N/A	N/A	2.72	7.8E-266	6,117	13,353	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs8106922	*TOMM40*	19	45,401,666	G	A	0.68	5.4E-39	0.66	6.5E-27	0.79	1.7E-01	N/A	N/A	0.67	2.3E-65	6,117	13,353	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs405509	*APOE*	19	45,408,836	G	T	0.70	4.9E-37	1.38	5.3E-18	0.72	5.4E-02	N/A	N/A	0.71	6.4E-53	6,117	13,353	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs439401	*APOE*	19	45,414,451	T	C	0.72	2.7E-23	0.63	5.1E-31	0.47	1.9E-05	N/A	N/A	0.68	1.4E-46	5,509	11,965	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs5167	*APOC4*	19	45,448,465	G	T	1.17	3.4E-08	1.09	1.9E-02	1.29	1.4E-01	1.11	5.8E-01	1.14	2.8E-09	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs3760627	*CLPTM1*	19	45,457,180	C	T	1.15	4.0E-07	1.12	2.8E-03	1.25	1.7E-01	1.13	5.0E-01	1.14	2.0E-09	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs7257916	*CLPTM1*	19	45,482,884	C	T	0.89	7.8E-05	1.10	9.2E-03	0.85	3.1E-01	0.95	7.3E-01	0.89	1.3E-06	6,080	12,297	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs8111069	*CLPTM1*	19	45,483,438	C	A	1.16	6.1E-06	1.11	4.6E-03	1.23	2.4E-01	1.06	6.6E-01	1.14	6.3E-08	6,080	12,297	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs1114832	*LRRC68*	19	45,636,201	T	C	1.31	2.2E-09	1.12	4.6E-02	1.20	4.9E-01	2.18	4.7E-06	1.26	2.1E-11	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs10425074	*LRRC68*	19	45,640,124	G	A	1.15	1.9E-05	1.09	1.0E-01	0.91	6.0E-01	1.46	1.3E-03	1.14	8.1E-07	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs1048699	*LRRC68*	19	45,650,386	T	C	1.32	1.5E-09	1.17	9.4E-03	1.12	6.8E-01	2.20	6.0E-06	1.29	8.4E-13	6,688	13,685	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs2627641	*EXOC3L2*	19	45,708,758	G	A	1.15	3.9E-04	1.18	1.1E-03	1.29	2.4E-01	N/A	N/A	1.17	7.6E-07	5,509	11,965	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus
rs597668	*EXOC3L2*	19	45,708,888	C	T	1.16	5.2E-05	1.19	1.0E-03	1.29	2.4E-01	N/A	N/A	1.17	1.3E-07	6,117	13,353	No	SNP was not selected for Stage 2 as it is located at the *APOE* locus

Supplementary Table 3. Stage 2, 3 and meta-analysis results for the 12 SNPs tested in Stage 2

SNP	Closest Gene	CHR	BP	A1	A2	Stage 2		Stage 2 Sample Size		SNP significant at Bonferroni adjusted level (P<0.0042)?	Stage 3		Stage 3 Sample Size		SNP significant at Bonferroni adjusted level (P<0.0167)?	Meta-analysis of all data					Meta-analysis Sample Size	
						OR	P	Cases	Controls		OR	P	Cases	Controls		OR	95% CI	P	Cochran's Q Test P	I^2	Cases	Controls
rs3764650	*ABCA7*	19	1046520	G	T	1.28	1.9E-05	4896	4903	Yes	1.22	2.9E-07	7176	17754	Yes	1.23	1.18-1.30	4.5E-17	0.80	0	17683	34269
rs744373	*BIN1*	2	127894615	G	A	1.17	3.8E-05	4896	4903	Yes	-	-	-	-	-	1.17	1.12-1.21	2.6E-14	0.59	0	11584	17619
rs670139	*MS4A4E*	11	59971795	T	G	1.11	1.1E-03	4896	4903	Yes	1.06	3.2E-03	8224	21194	Yes	1.09	1.06-1.12	1.4E-09	0.55	0	19262	38024
rs3818361	*CR1*	1	207784968	A	G	1.14	1.4E-03	4896	4903	Yes	-	-	-	-	-	1.18	1.13-1.24	3.7E-14	0.26	22.3%	11584	18154
rs610932	*MS4A6A*	11	59939307	T	G	0.90	1.6E-03	4896	4903	Yes	0.91	2.1E-05	7312	19874	Yes	0.90	0.87-0.92	1.8E-14	0.17	29.7%	18990	38080
rs7191155	*IQCK*	16	19800213	C	T	0.94	1.5E-01	4896	4903	No	-	-	-	-	-	-	-	-	-	-	-	-
rs4782279	*IQCK*	16	19759007	C	A	0.95	1.9E-01	4896	4903	No	-	-	-	-	-	-	-	-	-	-	-	-
rs1858973	*IQCK*	16	19743649	C	T	0.95	2.1E-01	4896	4903	No	-	-	-	-	-	-	-	-	-	-	-	-
rs739565	*C16orf88*	16	19716505	A	G	1.02	5.5E-01	4896	4903	No	-	-	-	-	-	-	-	-	-	-	-	-
rs10501927	*CNTN5*	11	99757729	G	T	1.02	6.9E-01	4896	4903	No	-	-	-	-	-	-	-	-	-	-	-	-
rs10761558	*CDK1*	10	62523470	A	G	1.00	9.0E-01	4187	3932	No	-	-	-	-	-	-	-	-	-	-	-	-
rs3809278	*CUX2*	12	111725185	A	C	1.00	9.9E-01	4896	4903	No	-	-	-	-	-	-	-	-	-	-	-	-

Supplementary Table 4a. SNPxSNP interaction P-values

SNP	rs744373 (*BIN1*)	rs11136000 (*CLU*)	rs610932 (*MS4A*)	rs3851179 (*PICALM*)	rs3764650 (*ABCA7*)	rs429358 (*APOE*)
rs3818361 (*CR1*)	0.6607	0.4892	0.4572	0.1942	0.9913	0.9367
rs744373 (*BIN1*)		0.9979	0.9780	0.9331	0.4509	0.1270
rs11136000 (*CLU*)			0.4100	0.0613	0.5545	0.6737
rs610932 (*MS4A*)				0.2474	0.5479	0.5909
rs3851179 (*PICALM*)					0.4491	0.7350
rs3764650 (*ABCA7*)						0.6242

NB: Data calculated from GERAD1 sample.

Supplementary Table 4b. Logistic regression analyses with and without adjustment for the presence of at least one *APOE* e4 allele. Note that only samples with *APOE* genotypes were included in the analysis

SNP	Datset	Unadjusted for APOE			Adjusted for APOE		
		OR	95% CI	P	OR	95% CI	P
rs610932	GERAD1	0.86	0.79-0.92	8.0E-05	0.86	0.79-0.93	3.3E-04
	GERAD2	0.95	0.88-1.03	1.8E-01	0.95	0.87-1.03	1.8E-01
	EADI1	0.93	0.86-1.00	4.6E-02	0.94	0.86-1.02	1.0E-01
	EADI2	0.90	0.83-0.97	7.7E-03	0.89	0.82-0.97	6.6E-03
rs670139	GERAD1	1.16	1.06-1.27	9.5E-04	1.16	1.05-1.27	2.3E-03
	GERAD2	1.11	1.03-1.20	7.7E-03	1.12	1.03-1.22	6.8E-03
	EADI1	1.06	0.99-1.14	1.2E-01	1.05	0.97-1.13	2.2E-01
	EADI2	1.02	0.94-1.11	5.9E-01	1.02	0.94-1.12	6.4E-01
rs3764650	GERAD1	1.15	0.99-1.33	6.6E-02	1.11	0.95-1.29	2.0E-01
	GERAD2	1.31	1.14-1.50	1.1E-04	1.30	1.12-1.50	4.0E-04
	EADI1	1.21	1.08-1.37	1.0E-03	1.20	1.08-1.32	2.7E-03
	EADI2	1.31	1.15-1.50	8.7E-05	1.34	1.18-1.52	7.0E-06

Supplementary Table 5. Analysis of rs3764650, rs670139 and rs610932 in published expression quantitative trait loci (eQTL) datasets.

	Stranger et al. 2005 (ref 49)				Gibbs et al. 2010 (ref 50)									
	Gene	Probe	Lymphoblastoid Cell Line		Gene	Probe	Cerebellum		Frontal Cortex		PONS		Temporal Cortex	
SNP			Beta	P-Value			Beta	P-Value	Beta	P-Value	Beta	P-Value	Beta	P-Value
rs3764650	***ABCA7***	GI_15451836-I	-0.009600	0.568	***ABCA7***	ILMN_1660203	-	-	-	-	-	-	-2.904	0.3897
		GI_15451837-A	0.037000	0.533	***ABCA7***	ILMN_1729894	-	-	-	-	-	-	0.997	0.7575
rs670139	***MS4A6A***	GI_23238233-A	0.003962	0.9149	***MS4A6A***	ILMN_1721035	0.1022	0.0789	0.02031	0.6744	0.1073	0.1113	0.1345	0.01461
	MS4A2	GI_23397640-S	-0.01104	0.3985	***MS4A6A***	ILMN_1797731	0.09749	0.06666	0.009008	0.836	0.09604	0.1494	0.09399	0.06527
	MS4A7	GI_23110999-S	0.03997	0.6868	***MS4A2***	ILMN_1806721	0.005871	0.6822	0.01349	0.3531	-0.00509	0.6967	-0.02791	0.06277
	MS4A3	GI_23110992-S	0.002893	0.8109	***MS4A7***	ILMN_1743932	-	-	0.03082	0.4309	0.2313	0.7232	0.06794	0.09215
	MS4A4A	GI_23110994-A	-0.01535	0.3443	***MS4A3***	ILMN_1726552	-	-	-	-	-	-	-0.00115	0.9245
	PLAC1L	GI_42476002-S	-0.0078	0.4747	***MS4A3***	ILMN_1751625	-	-	-	-	-	-	-0.014	0.4099
	MS4A6E	GI_23110998-S	-0.03553	0.5326	***MS4A4A***	ILMN_1741712	-	-	-	-	-	-	-0.00201	0.9129
					PLAC1L	ILMN_1757220	-	-	-	-	-	-	-0.01391	0.2999
rs610932	***MS4A6A***	GI_23238233-A	-0.02596	0.4978	***MS4A6A***	ILMN_1721035	-0.1298	0.01917	-0.06277	0.1781	-0.1068	0.101	-0.1229	0.02279
	MS4A2	GI_23397640-S	-0.00338	0.8032	***MS4A6A***	ILMN_1797731	-0.1239	0.01431	-0.05795	0.1669	-0.09928	0.1232	-0.1002	0.04446
	MS4A7	GI_23110999-S	-0.01259	0.9024	***MS4A2***	ILMN_1806721	0.004206	0.7592	-0.00184	0.8959	0.01337	0.2885	0.02492	0.0899
	MS4A3	GI_23110992-S	0.009299	0.4564	***MS4A7***	ILMN_1743932	-	-	-0.03136	0.4072	-0.02838	0.6533	-0.05286	0.1814
	MS4A4A	GI_23110994-A	-0.01123	0.5048	***MS4A3***	ILMN_1726552	-	-	-	-	-	-	0.01008	0.3962
	PLAC1L	GI_42476002-S	0.007844	0.4874	***MS4A3***	ILMN_1751625	-	-	-	-	-	-	0.01783	0.283
	MS4A6E	GI_23110998-S	-0.05092	0.3869	***MS4A4A***	ILMN_1741712	-	-	-	-	-	-	0.01617	0.3682
					PLAC1L	ILMN_1757220	-	-	-	-	-	-	0.02278	0.0816

Supplementary Note for "Common variants in ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease.".

Sample Description

Stage 1 Samples

GERAD1

The GERAD1[1] sample comprised up to 3941 AD cases and 7848 controls. This sample included 4113 cases and 1602 elderly screened controls genotyped at the Sanger Institute on the Illumina 610-quad chip, referred to collectively hereafter as the 610 group. These samples were recruited by the Medical Research Council (MRC) Genetic Resource for AD (Cardiff University; Institute of Psychiatry, London; Cambridge University; Trinity College Dublin), the Alzheimer's Research Trust (ART) Collaboration (University of Nottingham; University of Manchester; University of Southampton; University of Bristol; Queen's University Belfast; the Oxford Project to Investigate Memory and Ageing (OPTIMA), Oxford University); Washington University, St Louis, United States; MRC PRION Unit, University College London; London and the South East Region AD project (LASER-AD), University College London; Competence Network of Dementia (CND) and Department of Psychiatry, University of Bonn, Germany and the National Institute of Mental Health (NIMH) AD Genetics Initiative. These data were combined with data from 844 AD cases and 1255 elderly screened controls ascertained by the Mayo Clinic, Jacksonville, Florida; Mayo Clinic, Rochester, Minnesota; and the Mayo Brain Bank (Mayo1 dataset). All AD cases met criteria for either probable (NINCDS-ADRDA[2], DSM-IV) or definite (CERAD[3]) AD. All elderly controls were screened for dementia using the MMSE or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. A total of 6,825 unscreened population controls were included GERAD1. These were drawn from large existing cohorts with available GWAS data, including the 1958 British Birth Cohort (1958BC) (http://www.b58cgene.sgul.ac.uk), NINDS funded neurogenetics collection at Coriell Cell Repositories (Coriell) (see http://ccr.coriell.org/), the KORA F4 Study[4], Heinz Nixdorf Recall Study[5,6] and ALS Controls. (NB: KORA samples were also included in the German Alzheimer's disease Integrated Genome Research

Network (AD-IG) GWAS, therefore for SNPs that were carried forward to Stage 2, KORA samples were removed from the GERAD1 analysis).

EADI1

The EADI1 sample (2025 AD cases and 5328 controls) have been described in detail previously[7]. Briefly, AD cases were ascertained by neurologists from Bordeaux, Dijon, Lille, Montpellier, Paris, Rouen, and were identified as French Caucasian[8]. Clinical diagnosis of probable AD was established according to DSM-III-R and NINCDS-ADRDA criteria[2]. Controls were selected from the 3C Study[9]. The 3C Study is a population-based, prospective study of the relationship between vascular factors and dementia. It has been carried out in three French cities: Bordeaux (southwest France), Montpellier (south France) and Dijon (central eastern France). A sample of non-institutionalised, over-65 subjects was randomly selected from the electoral rolls of each city. Between January 1999 and March 2001, 9686 subjects meeting the inclusion criteria agreed to participate. Following recruitment, 392 subjects withdrew from the study. Thus, 9294 subjects were finally included in the study (2104 in Bordeaux, 4931 in Dijon and 2259 in Montpellier). At the baseline clinical examination, blood samples were obtained from 8414 individuals who were representative of the source population. Trained psychologists administered a battery of neuropsychological tests, including the MMSE. All participants in Bordeaux and Montpellier were also examined by a neurologist at baseline. All control participants were followed for 4 years and did not develop dementia during this time period.

ADNI

Following quality control (QC) filters applied in this study, the Alzheimer's Disease Neuroimaging Initiative (ADNI; see www.loni.ucla.edu/ADNI) sample included 151 AD cases and 177 controls. These samples have been described in detail elsewhere[10]. ADNI is a multi-site observational study including AD, mild cognitive impairment (MCI), and elderly individuals with normal cognition assessing clinical and cognitive measures, MRI and PET scans and blood and CNS biomarkers. AD cases were between the ages of 55–90, with an MMSE score of

20–26 inclusive and meeting NINCDS-ADRDA criteria for probable AD[2], and having an MRI consistent with the diagnosis of AD. Control individuals were screened for dementia using the MMSE, adopting a cut off of 27 or above.

TGEN

The Translational Genomics Research Institute (TGEN) GWA study included 861 AD cases and 550 controls. Following QC applied in this study 571 AD cases and 332 controls were included in subsequent analyses. These samples have been described previously[11]. Briefly, the sample comprised two neuropathological cohorts of brain doners (Cases n=458; Controls n=274) and a 'clinical cohort' (Cases n=113; Controls n=58). All participants were at least 65 years old at the time of their death or last clinical assessment. For the two neuropathological cohorts, brain tissue for DNA extraction, neuropathological diagnoses and data were supplied by investigators from 20 of the National Institute on Aging (NIA)-sponsored Alzheimer's Disease Centers (ADCs) (in accordance with agreements with the NIA, the ADCs, and the National Alzheimer's Coordinating Center) and from the Netherlands Brain Bank. For the clinical cohort, DNA extracted from blood, clinical diagnoses and data from subjects assessed in Rochester, MN were supplied by investigators from the Mayo Clinic. Neuropathological AD cases satisfied clinical and neuropathological criteria for LOAD. Brain donor controls did not have significant cognitive impairment or significant neuropathological features of AD. Clinical cases satisfied NINCS-ADRDA criteria for probable AD. Clinical controls did not have clinically significant cognitive impairment.

Stage 1 included a total of up to 6688 AD cases and 13685 controls. All AD cases were diagnosed according NINCDS-ADRDA[2], DSM-IV or CERAD[3] criteria for either probable or definite AD. AD cases were predominantly female (62.4%). The mean age at disease onset and ascertainment in AD cases were 71.6 and 77.3 years, respectively. Stage 1 included a total of 7915 aged (≥60 years), screened controls (59.9% female; mean age at collection, 74.5 years) and 5770 population based, unscreened controls from the GERAD1 study (50.8% female, mean age at collection 48.6 years).

Stage 2 Samples

Stage 2 included individual genotyping of the GERAD2 sample (3262 cases and 3320 controls) and *in silico* replication in the deCODE and AD-IG GWAS datasets (925 cases and 612 controls; 709 cases and 971 controls respectively).

GERAD2

The GERAD2 sample comprised 3262 AD cases and 3320 controls. These samples were ascertained by the Medical Research Council (MRC) Genetic Resource for AD (Cardiff University; Institute of Psychiatry, London; Cambridge University; Trinity College Dublin), the Alzheimer's Research Trust (ART) Collaboration (University of Nottingham; University of Manchester; University of Southampton; University of Bristol; Queen's University Belfast), Washington University, St Louis, United States; MRC PRION Unit, University College London; London and the South East Region AD project (LASER-AD), University College London; Competence Network of Dementia (CND) and Department of Psychiatry, University of Bonn, Germany and the National Institute of Mental Health (NIMH)AD Genetics Initiative, Aristotle University of Thessaloniki; the Caerphilly Prospective Study; the University of Munich; and a Belgian sample derived from a prospective clinical study at the Memory Clinic and Department of Neurology, ZNA Middelheim, Antwerpen[12]. All AD cases met criteria for either probable (NINCDS-ADRDA[2], DSM-IV) or definite (CERAD[3]) AD. Control subjects were aged (>60 years of age) and predominantly screened for dementia (95.5%).

Control subjects from the MRC Genetic Resource for AD, Queen's University Belfast (ART collaboration) and Belgium were screened for cognitive decline using the MMSE[13] or ADAS-Cog. Controls ascertained by the University of Bristol and University of Nottingham, as part of the ART collaboration, were neuropathologically assessed and were dementia-free according to CERAD criteria[3]. The control group from Munich was a population-based random sample from Munich, Germany. Individuals were screened for dementia and other neuropsychiatric disorders using a comprehensive interview including the SCID[14]. Additionally, the Family History Assessment Module was conducted to exclude psychiatric disorders including dementias among first-degree relatives.

A neurological examination was also conducted to exclude subjects with current CNS impairment. Individuals older than 60 years were screened for cognitive impairment using the Mini Mental Status Examination[13]. The control subjects from the University of Bonn were recruited within the German Study on Aging, Cognition and Dementia (AgeCoDe). Cognitive impairment was ruled out in those individuals with the Structured Interview for Diagnosis of Dementia of Alzheimer type, Multi-infarct Dementia and Dementia of other Aetiology according to DSM-IV and ICD-10 (SIDAM)[15], which includes a cognitive battery. All control subjects performed within the normal age, sex and education adjusted norms on this cognitive battery[16]. Greek controls were unrelated carers of AD patients or recruited from the Greek blood donation service.

German Alzheimer's disease Integrated Genome Research Network GWAS

This study included 709 AD cases and 971 controls of German extraction from the Alzheimer's disease Integrated Genome Research Network (AD-IG) GWA study, which has been previously reported in part[17]. All patients were recruited by specialists at the outpatient clinic of the Technische Universität München. AD cases were diagnosed according to NINCDS-ADRDA[2] criteria for probable AD. Cognitive performance was assessed using standard neuropsychological tests, such as the Cambridge Cognitive Examination[18] or a test endorsed by the Consortium to Establish a Registry for Alzheimer's disease[19] which includes the Mini Mental State Examination[13]. Controls were drawn from two population-based cohorts: the PopGen Biobank, run by the Universitätsklinikum Schleswig-Holstein and the KORA F4 Study[4].

deCODE

The deCODE sample comprised 925 AD cases and 612 controls. AD cases were enrolled through the Memory Clinic at Landspitali University Hospital, to which all Icelanders suffering from cognitive decline are referred. Additional individuals were selected for enrolment based on an encrypted list of 3,188 patients with cognitive impairment compiled from Icelandic hospitals and nursing homes, or based on phenotype information obtained through the Resident Assessment Instrument (RAI). Individuals diagnosed with definite,

probable or possible AD according to NINCDS-ADRDA criteria were included in the study (N = 823). Individuals recruited based on RAI data met ICD-10 criteria for Alzheimer's disease (N = 102).

Controls were characterized based on phenotype information from RAI, more specifically the Minimum Data Set for Nursing Homes (MDS-NH)[20] and Home Care (MDS-HC)[21]. Individuals with a score of zero on the Cognitive Performance Scale (CPS)[22] at age 85 or older (N = 612) were used as cognitively intact controls.

All samples were collected through studies approved by the Data Protection commission and the National Bioethics Committee of Iceland. All participating individuals, or their guardians, gave their informed consent before blood samples were drawn, and all sample identifiers were encrypted in accordance with the regulations of the Icelandic Data Protection Committee.

Stage 2 included a total of up to 4896 AD cases and 4903 controls. All cases were diagnosed according NINCDS-ADRDA[2], DSM-IV or CERAD[3] criteria for either possible, probable or definite AD. AD cases were predominantly female (63.4%). The mean age at disease onset and ascertainment in AD cases were 72.3 and 76.8 years, respectively. The stage 2 control group (55.1% female, mean age at ascertainment 70.0 years) were predominantly aged (≥60 years) and screened for dementia (77.2%).

Stage 3 Sample

EADI2

EADI2 case-control samples were obtained from centres in Finland (1 centre)[23], Spain (3 centres)[24,25] and Italy (10 centres)[26-35]. Clinical diagnoses of probable AD were all established according to the DSM-III-R and NINCDS-ADRDA criteria[2]. Controls were defined as subjects without DMS-III-R dementia criteria and with integrity of their cognitive functions (MMS>25). Written informed consent was obtained as described above, and the study protocols for all populations were reviewed and approved by the appropriate Institutional review boards of each country.

Mayo2

The Mayo2 case-control series consisted of Caucasian subjects from the United States ascertained at the Mayo Clinic Jacksonville, Mayo Clinic Rochester, and in the Mayo Clinic autopsy-confirmed sample. Additional Caucasian subjects from the United States were obtained through the National Cell Repository for Alzheimer's Disease (NCRAD), and European Caucasian subjects were obtained from Norway[36], Poland[37], and from six research institutes in the United Kingdom that are part of the Alzheimer's Research Trust Network (ART). AD cases ascertained at the Mayo Clinic Jacksonville, Mayo Clinic Rochester and NCRAD were diagnosed according to NINCDS-ADRDA criteria for possible or probable AD. Controls had a Clinical Dementia Rating[38] scale score of 0. Cases from the Mayo autopsy series were diagnosed according to NINCDS-ADRDA criteria for definite AD and had a Braak stage score of 4 or greater. Brains employed as controls had a Braak score of 2.5 or lower and were free from AD pathology at autopsy. AD cases ascertained in Norway were diagnosed according to NINCDS-ADRDA criteria for possible or probable AD. Controls were determined to be cognitively intact using a brief clinical interview and did not have a first degree relative with dementia. A proportion were screened for cognitive impairment using the MMSE[13]. AD cases in the Polish cohort were diagnosed with probable AD according to NINCDS-ADRDA criteria for AD. Polish controls were screened for cognitive impairment and did not show symptoms of dementia. Although the ART samples used in this follow-up do not overlap with those employed in Stage 1 of the study (genotyped as part of the GERAD1 GWAS[1] the same subject/sample ascertainment methodology was followed. The ART series included here are from Bristol, University of Leeds, Manchester, Nottingham, Oxford and Southampton. The Mayo2 cohort comprised 880 AD cases and 1332 controls genotyped as part of the GWAS study reported by Carrasquillo and colleagues[39] which were included in Stage 1 of this study. These individuals were only genotyped and used in the analysis of rs670139 as this SNP was not genotyped as part of the GWAS and these data were not included in Stage 1 of this study. Approval was obtained from the ethics committee or institutional review board of each institution responsible for the ascertainment and collection

of samples. Written informed consent was obtained for all individuals that participated in this study. Samples used in this study do not overlap with those included in the Harold et al. 1 publication.

CHARGE

The CHARGE[40] dataset analyzed here includes four large, prospective, community-based cohort studies that have genome-wide association data coupled with extensive data on multiple phenotypes[41]: the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), the Rotterdam Study, and the Age, Gene/Environment Susceptibility – Reykjavik Study (AGES-RS). A neurology working-group arrived at a consensus on phenotype harmonization, covariate selection and analytic plans for within-study analyses and meta-analysis of results[42]. Consent procedures, examination and surveillance components, data security, genotyping protocols and study design at each study were approved by a local Institutional Review Board. (NB: Stage 1 of the CHARGE GWA study reported by Seshadri and colleagues included data from the Mayo[39] and the TGEN[11] GWA studies. These data overlap with samples used in Stage 1 of this study and were removed from analyses of the CHARGE dataset in this study).

Clinical characteristics of all samples can be found in Supplementary Table 1. An overview of the study design is shown in Figure 1 of the manuscript.

All individuals included in these analyses have provided consent to take part in genetic association studies. We have obtained ethical approval to use these samples to search for susceptibility genes for Alzheimer's disease (MREC 04/09/030; Amendment 2 and 4; approved 27 July 2007).

Genotyping and association analysis: GWA datasets

GERAD1

Individuals were genotyped using either the Illumina 610-quad, the HumanHap550 or the HumanHap300 array. QC and analysis has been described in detail elsewhere[1]. Briefly, 529205 autosomal SNPs were tested for association with Alzheimer's disease using logistic regression assuming an additive model.

Covariates were included in the logistic regression analysis to allow for geographical region and chip. The first four principal components extracted from an EIGENSTRAT analysis were also included as covariates.

EADI1

Individuals were genotyped using the Illumina 610-quad array. QC and analysis has been described in detail elsewhere[7]. Briefly, 537029 autosomal SNPs were tested for association with Alzheimer's disease using logistic regression assuming an additive model, including age, sex and principal components to account for possible population stratification as covariates.

ADNI

Individuals were genotyped using the Illumina 610-quad array. No quality control had been performed on the publicly available ADNI dataset, therefore the data were subjected to QC-filtering prior to analysis by logistic regression. This included retaining individuals with missing genotype rates < 0.01, with mean autosomal heterozygosity between 0.32 and 0.34, and with mean X-chromosome heterozygosity either <0.02 for males, or between 0.25 and 0.40 for females. 523539 SNPs with a minor allele frequency > 0.01, a missing data rate <0.03 and a Hardy-Weinberg $P>1 \times 10^{-4}$ were retained in the study. These SNPs were tested for association with Alzheimer's disease using logistic regression assuming an additive model.

TGEN

Individuals were genotyped using the Affymetrix 500K array. Although some quality control had been performed on the publicly available TGEN data, additional filters were applied. We removed 172 individuals with missing genotype rates > 0.03. We also applied a filter based on mean autosomal heterozygosity, excluding 302 individuals with values above or below empirically determined thresholds. All individuals passing these QC filters were examined for potential genetic relatedness by calculating identity-by-descent (IBD) estimates for all possible pairs of individuals in PLINK, and removing one of each pair with an IBD estimate >0.125 (the level expected for first cousins). As

a result, 1 individual was excluded. We also sought to detect non-European ancestry. To this end, TGEN genotype data was merged with genotypes at the same SNPs from 210 unrelated European (CEU), Asian (CHB and JPT) and Yoruban (YRI) samples from the HapMap project. Subsequent to removing SNPs in extensive regions of LD (Chr 5:44–51.5 Mb; Chr 6: 25–33.5 Mb; Chr 8: 8–12 Mb; Chr 11: 45–57 Mb), we further excluded SNPs if any pair within a 50-SNP window had $r^2 > 0.2$. Genome-wide average identity-by-state (IBS) distance was calculated in PLINK between each pair of individuals in the resulting dataset. The resulting matrix of IBS distances was used as input for classical multidimensional scaling (MDS). When the first two dimensions were extracted and plotted against each other, three clusters were observed as corresponding to the European, Asian and Yoruban samples. Four samples appeared to be ethnic outliers from the European cluster and were excluded from further analysis. We assessed population structure within the data using principal components analysis as implemented in EIGENSTRAT to infer continuous axes of genetic variation. Eigenvectors were calculated based on the previously described LD-pruned subset. The EIGENSTRAT program also identifies genetic outliers, which are defined as individuals whose ancestry is at least 6 standard deviations from the mean on one of the top ten axes of variation. As a result of this analysis, 29 outliers were identified and excluded. SNPs with a minor allele frequency < 0.01, a missing data rate >0.03 and a Hardy-Weinberg $P<1 \times 10^{-4}$ were excluded. Following QC, 571 Alzheimer's disease cases, 332 controls and 301243 SNPs were included in the analysis. As there is little overlap between the Affymetrix 500K array and the Illumina 610 array, unobserved genotypes were imputed with MACH v.1.0, using haplotypes released from initial low coverage sequencing of 112 European ancestry samples in the 1000 genomes project (ftp://ftp.sanger.ac.uk/pub/1000genomes/REL-0908/LowCov/) as a reference sample. Imputation generated data for >8.2 million SNPs. These were subsequently filtered to exclude SNPs with MAF<0.01 or RSQR<0.3. SNPs not present on the Illumina 610 array were also excluded. 457509 autosomal SNPs were tested for association with Alzheimer's disease using logistic regression assuming an additive model. A covariate was included to distinguish between

country of origin, *i.e.* USA or the Netherlands. The first principal component from the EIGENSTRAT analysis was also included as a covariate.

AD-IG

Genotyping was performed by Illumina (San Diego, CA, USA) using their Sentrix HumanHap550 Genotyping BeadChip. Eighteen individuals with missing genotype rates > 0.3 were removed. All individuals passing this QC filter were examined for potential sex misclassification in PLINK. Seventeen individuals with differences in reported and estimated sex on the X-chromosome were excluded. Genome-wide average identity-by-state (IBS) distance was calculated in PLINK between each pair of individuals in the resulting dataset and removing one of each pair with an IBS estimated distance >0.985 (the level expected for identical individuals and monozygotic twins). As a result, 21 individuals were excluded. The resulting matrix of IBS distances was used as input for classical multidimensional scaling (MDS) to assess population structure[43]. When the first four dimensions were extracted and plotted against each other only one cluster without any outliers was observed in accordance with the origin and ethnic background of the German sample. To account further for any hidden population stratification the first two dimensions from the MDS approach were used as covariates in the logistic regression analysis[44]. SNPs with a minor allele frequency < 0.01, a call rate <0.8 and a Hardy-Weinberg $P < 1 \times 10^{-3}$ were excluded. Following QC, 709 Alzheimer's disease cases, 971 controls and 521102 SNPs were included in the analysis. SNPs were tested for association with Alzheimer's disease using logistic regression assuming an additive model. Age and sex were also included as covariates, along with the first two components from the MDS analysis.

deCODE

Individuals were genotyped using Illumina HumanHap300, Illumina HumanHap300-duo or Illumina HumanCNV370-duo BeadChips. Samples with yield below 98%, a higher-quality duplicate in the data set or evidence of non-European ancestry based on results from STRUCTURE[45] were excluded. SNPs were deemed unusable if they had yield below 95%, HWE $P < 1 \times 10^{-6}$ or an allele

frequency difference between chips with $P < 1 \times 10^{-6}$. For genotyped SNPs, analysis was carried out using a previously-described likelihood procedure[45]. Imputation was performed using IMPUTE[46] with the HapMap CEU samples as a training set or, for rs10761558, using an IMPUTE-like algorithm developed at deCODE and a long-range-phased[47] Icelandic training set typed using Illumina Human1M BeadChips. For analysis of imputed genotype probabilities, the likelihood method in SNPTEST was used. All results were corrected for relatedness and possible population stratification using genomic control[48]. The inflation factor was 1.13.

CHARGE

For analysis of prevalent events in the four cohorts, SNPs were tested for association with Alzheimer's disease using logistic regression assuming an additive model. For the analysis of incident events in the cohorts, participants who were free of dementia entered the analysis at the time of the DNA sample collection and were followed until the development of incident AD; participants were censored at death, at the time of their last follow-up examination or health status update when they were known to be free of clinical dementia, and when they developed dementia due to an alternate cause. Cox proportional hazards models were used to calculate hazard ratios with corresponding 95% confidence intervals after ensuring that assumptions of proportionality of hazards were met. In the CHS, FHS, and Rotterdam studies, controls contributed one set of person-years to the prevalent analysis and a second, non-overlapping set of person-years to the incident analyses. Under the martingale property of Cox models, the two analyses are independent and their independence was confirmed in simulation studies. Primary analyses were adjusted for age and sex and any evidence of population stratification. An inverse variance-weighted meta-analysis combined results from seven discrete sources: incident AD in the CHS, FHS, and Rotterdam cohorts, prevalent AD in the AGES, CHS, FHS, and Rotterdam cohorts. Note that in stage 1 of their GWA study, Seshadri *et al*.[40] meta-analyzed data from the CHARGE dataset, plus data from the Mayo sample from Carrasquillo *et al*.[39] (which also forms part of GERAD1), plus data from the TGEN sample. However, only the CHARGE summary statistics are included from this

group to prevent any overlap. Also note that as the CHARGE data was generated using multiple platforms, imputation had been performed to bridge any gaps.[40]

Genotyping and association analysis: Non-GWAS Samples

GERAD2

Genotyping was performed using the MassARRAY and iPlexGOLD systems (Sequenom™) according to manufacturer's recommendations. All assays were initially optimized by genotyping DNA from 30 CEPH parent-offspring trios (Utah residents with ancestry from northern and western Europe: CEU), also genotyped by the HapMap project. All plates for genotyping contained a mixture of cases, controls, blanks, and CEU samples. All Sequenom cluster-plots were visually inspected and double-genotyping was performed for every assay. Genotypes were called blind to sample identity, affected status, and blind to the other rater. Assays were only considered suitable for analysis if genotypes of CEU individuals were concordant with those in HapMap, where available. Genotypes from controls were tested for departure from Hardy-Weinberg equilibrium (HWE); rs10501927 alone showed nominally significant evidence of departure from HWE (P=0.03). GERAD2 data were analyzed by logistic regression assuming an additive model including covariates to distinguish between (i) the UK sample (ii) the Belgium sample (iii) the Bonn sample (iv) the Munich sample and (v) the Greece sample.

EADI2

EADI2 genotyping was performed using Sequenom assays. The primer and probe sequences for the genotyping assays are available upon request. In order to avoid any genotyping bias, cases and controls were randomly mixed when genotyping, and laboratory personnel were blinded to case/control status. Genotyping success rate was at least 95%, and no departure from Hardy-Weinberg equilibrium was observed for the markers. Statistical analyses was performed in each country (Finland, Italy and Spain) under an additive genetic model using logistic regression taking account of age, sex and disease status using SAS software release 9.1 (SAS Institute, Cary, NC). Inverse variance-weighted meta-analysis was used to combine results from the three cohorts.

MAYO2

All genotyping was performed at the Mayo Clinic in Jacksonville using TaqMan® SNP Genotyping Assays in an ABI PRISM® 7900HT Sequence Detection System with 384-Well Block Module from Applied Biosystems, California, USA. The genotype data was analyzed using the SDS software version 2.2.3 (Applied Biosystems, California, USA). The Mayo2 data data were analyzed by logistic regression assuming an additive model including covariates to distinguish between (i) the US sample (ii) the UK sample (iii) the Norweigen sample and (iv) the Polish sample.

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